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An Assessment of HCG from Day 2 Spent Embryo Culture Media and its Relation to Embryo Developmental Potential in Females Undergoing IVF Using Different Ovulation Triggers (HCG, Decapeptyl Alone or Dual Trigger)

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Abstract--- *Infertility is one of the major medical difficulties in the world caused by genetic or epigenetic causes, or both, which has led to constant research and studies in the field of assisted reproductive technology. Several stimulation protocols are available for controlled ovarian hyper stimulation in in-vitro fertilization and Intracytoplasmic sperm injection. To compare the effect HCG and dual triggering for final oocyte maturation on HCG level in embryo spent culture media and its effect on embryo development and quality. In order to assess the health and developmental ability of individual embryo the needs for no invasive processes in addition to morphological assessment of embryo have increased like HCG level in culture media.*

Keywords--- *Sterility, Genetic causes, Fertilization, Mature Eggs.*

I. INTRODUCTION

The most critical phenomenon for continued existence of man-kind is the ability to reproduce. Defects in reproduction that may involve both the male and female partners result in the inability to procreate which is known as infertility.

The clinical definition of infertility used by the World Health Organization (WHO) is ‘‘a disease of the reproductive system defined by the failure to achieve a clinical pregnancy after 12 months or more of regular unprotected sexual intercourse ’’While the WHO’s epidemiologic definition is ‘women of reproductive age at risk of becoming pregnant who reported unsuccessful trials for a pregnancy for more than two years’ (Singh, et al., 2017). Clinical definitions are designed for early detection and treatment of infertility (Mascarenhas et al., 2012).

Infertility can be due to any abnormality in the female or male reproductive system. In most cases, the aetiology is distributed quite equally among male factors, ovarian dysfunction, and tubal factors. A smaller percentage of cases are caused by endometriosis, uterine or cervical factors, or other causes. In approximately one fourth of couples, the cause is uncertain and is referred to as “unexplained infertility”. The aetiology is multifactorial in some couples (Idowu et al., 2017).

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The aim of this to detect hCG in spent embryo culture media at day 2 after intracytoplasmic sperm injection and to assess the relationship of HCG to embryo development in different ovulation triggers (HCG, alon or dual trigger)and compare between them.

The Treatment of Infertility Includes

Fertility drugs are frequently used alone as initial treatment to induce ovulation. If they fail as individual therapy, they may be used with assisted reproductive procedures, such as in vitro fertilization, to produce multiple eggs, a process called *superovulation*. According to the American Society for Reproductive Medicine, fertility drugs can be divided into three main categories:

1. Medications for ovarian stimulation. Clomiphene (Clomid, Serophene); letrozole (Femara), follicle stimulating hormone (FSH) [Follistim, Gonal-F, Bravelle]; human menopausal gonadotrophin (hMG) (Humegon, Repronex, Menopur); luteneizing hormone (LH) [Luveris]
2. Medications for oocyte maturation. Human chorionic gonadotropin (hCG) [Profasi, APL, Pregnyl, Novarel, Ovitrelle)
3. Medications to prevent premature ovulation. GnRh agonists (Lupron and Synarel); GnRh antagonists (Antagon, Cetrotide) (Usadi, et al., 2015).

Assisted reproduction includes all the methods used for fertilization, which is not achieved through sexual inter course. Intracytoplasmic sperm injection (ICSI) is, currently, the most efficient modification of micromanipulation-assisted fertilization, whereby one spermatozoon is selected, aspirated into a microinjection needle, and injected into the oocyte cytoplasm (Rahman et al., 2010).

Forty infertile females who were undergoing controlled ovarian hyper stimulation for ICSI cycle were prospectively employed according to specific principles for this study in High Institute of Infertility Diagnosis and Assisted Reproductive Technology / AL- Nahrain University during the period from July 2019 until January 2020. They were divided into two groups, 20 of them were treated with HCG trigger and 20 patients were treated with dual trigger. They subjected for IVF- ICSI followed by assessment of oocyte and resulting embryo quality and measurement of HCG hormone in spent embryo culture media after embryo transfer.

Samples Collection and Oocytes Assessment

The follicular fluid was collected from the very first single aspirated follicle of the infertile females undergoing ICSI cycles. Oocyte development, fertilization outcome, and embryo quality three days after insemination were recorded and evaluated. The oocytes were assessed after denuding and grouped according to their nuclear maturity and morphology status into:

1. An immature oocyte may be considered at germinal vesicle stage of maturity in which the organelles condensed centrally within the cytoplasm.
2. A metaphase I (MI) oocyte was defined as an oocyte with no germinal vesicle (GV) and no polar body (PB) in perivetilline space.

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3. A metaphase II (MII) oocyte was defined according to criteria put by Swain and Pool, as simply; a single PB, a 'normal looking' cytoplasm, an appropriate zona thickness, and proper perivetilline space (Leary, C., 2015). And by the Istanbul consensus workshop on embryo assessment as; a spherical structure, enclosed by a uniform zona pellucida with a uniform translucent cytoplasm free of inclusions and a size appropriate PB (Balaban, B., 2017.).

The percentage of mature oocytes was calculated (Maturity index) following this formula Maturity index= (No. of mature oocytes (MII)/ Total number of oocytes retrieved) ×100 (Mehri, et al. 2014).

Abnormal or degenerated oocytes collected were not inseminated by ICSI and were not included in the analysis. These were defined as oocytes that were exceptionally large, or oocytes with exceptionally large PBs, multiple large vacuoles, clusterings of smooth endoplasmic reticulum in the cytoplasm, or a diffused, darkened or highly irregular cytoplasm (Oocytes, M.I.S.H., 2018).

II. RESULTS

The results showed highly significant difference ($p<0.001$) in number of dominant follicles, significant difference ($p<0.05$) in number of oocytes retrieved and significant difference ($p<0.05$) in number of metaphase II oocytes or maturity index, between HCG group and dual treated groups. On the other hand, the level of HCG in culture media increase the good quality embryo showed significant difference ($p<0.05$).

Clinical Presentation

The start of ovulation can be detected by signs. Because the signs are not readily discernible by people other than the female, humans are said to have a concealed ovulation. In many animal species there are distinctive signals indicating the period when the female is fertile. Several explanations have been proposed to explain concealed ovulation in humans.

Females near ovulation experience changes in the cervical mucus, and in their basal body temperature. Furthermore, many females experience secondary fertility signs including Mittelschmerz (pain associated with ovulation) and a heightened sense of smell, and can sense the precise moment of ovulation (Briden, L., 2017).

Many females experience heightened sexual desire in the several days immediately before ovulation. One study concluded that females subtly improve their facial attractiveness during ovulation.

Figure 1: Chance of Fertilization by Day Relative to Ovulation (Beall, et al. 2013)

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Symptoms related to the onset of ovulation, the moment of ovulation and the body's process of beginning and ending the menstrual cycle vary in intensity with each female but are fundamentally the same.

The charting of such symptoms — primarily basal body temperature, mittelschmerz and cervical position — is referred to as the sympto-thermal method of fertility awareness, which allow auto-diagnosis by a female of her state of ovulation.

Once training has been given by a suitable authority, fertility charts can be completed on a cycle-by-cycle basis to show ovulation. This gives the possibility of using the data to predict fertility for natural contraception and pregnancy planning.

Hormonal Assay

Table 1 and figure 2 shown the hormonal assay of the studied groups (HCG and DUAL groups) , also expressed in mean plus minus standard deviation and the results was respectively as following; for FSH (8.5 ± 5.5 and 8.09 ± 2.6) , for LH (4.6 ± 3.7 and 4.3 ± 1.3) ,for E2 (33.2 ± 15.1 and 44.7 ± 32.3). There was no significant differences in FSH, LH and E2 between the 2 studied groups (P= 0.762, P= 0.753 and P= 0.158) respectively.

Table 1: Demografic And Hormonal Data in the Studied Groups

	Grouping	**Mean**	**S.D**	**S.E of Mean**	**P Value**
Age	HCG	31.05	7.82	1.75	0.647
	DUAL	32.10	6.53	1.46	
BMI	HCG	28.84	3.43	0.77	0.299
	DUAL	27.65	3.74	0.84	
FSH	HCG	8.50	5.52	1.23	0.762
	DUAL	8.09	2.59	0.58	
LH	HCG	4.60	3.74	0.84	0.753
	DUAL	4.32	1.31	0.29	
E2	HCG	33.22	15.12	3.38	0.158
	DUAL	44.71	32.35	7.23	

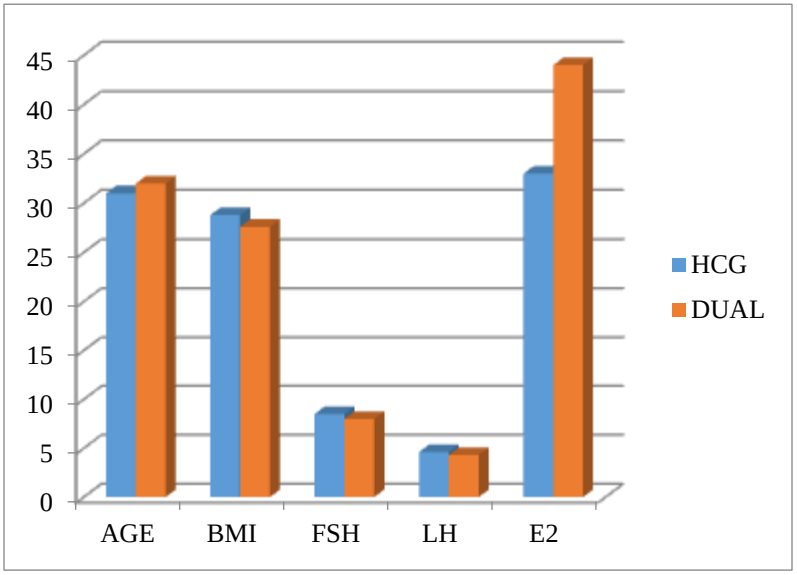

Figure 2: Demografic and Hormonal Data in the Studied Groups

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Correlation with Embryo Quality

Table 2 and graph 3 demonstrated the correlation between HCG levels in the culture media and embryo quality and the results show a positive significant correlation in HCG level and number of (G1 and G2) embryos (r = 0.379 ,P= 0.016) ,but there was no significant correlation with the number of (G3 and G4) embryos (r = -0.001 ,p = 0.993).

Table 2: Correlation between HCG Level in Culture Media and ICSI Outcome

	GV	MI	MII	G1,2	G3,4
HCG level in culture media	0.208	0.222	0.210	0.379	- 0.001
P value	0.198	0.168	0.193	0.016	0.993

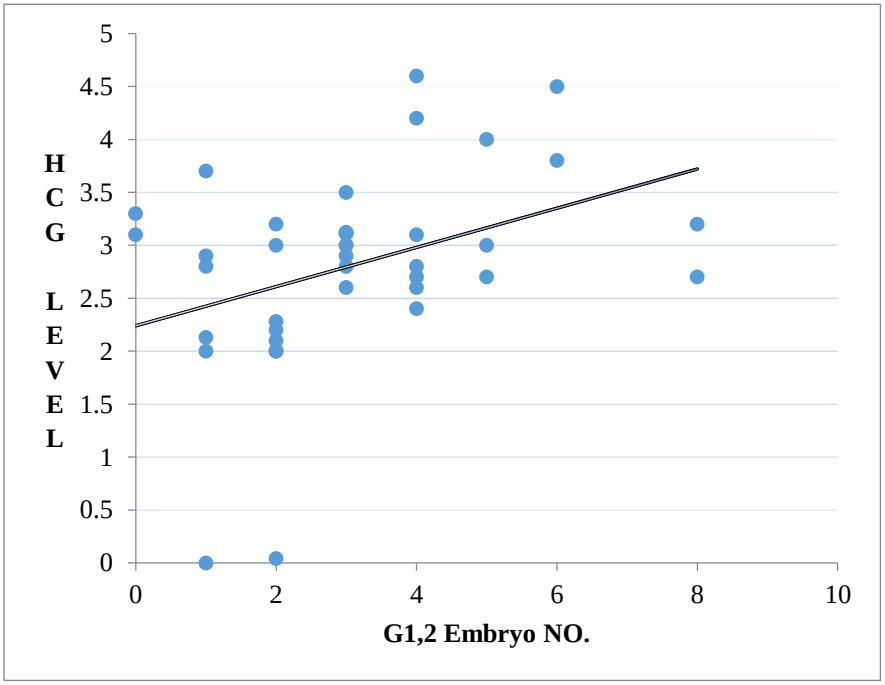

Figure 3: Correlation between HCG Level in Culture Media and (G1, 2) Embryo

III. CONCLUSION

The using of different types of ovulation triggers (HCG and Dual) effect on number of oocyte retrieval, oocyte quality or embryo quality according to morphological and molecular parameters and level of HCG in culture media also had effect on embryo development according to this retrospective study, the Dual Trigger used for induction of final oocyte maturation in normal responders, poor responders, and patients with immature oocytes, significantly improves the number of collected oocytes, mature oocytes, more then we use HCG alone. The elevation in the Level of HCG in culture media improve the embrio quality (G1, G2) embrio.

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